

10/563074

## SEQUENCE LISTING

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<110> WADA, Naoya  
 OKAMOTO, Takashi  
 TANIGAKI, Keiji  
 DOI, Hirofumi  
 KIKUCHI, Yasuhiro  
 IMAI, Kensaku

<120> Method for Inhibiting Telomerase Activity and Inhibitor Thereof

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<140> US Unassigned

<141> 2005-12-29

<150> JP P2004-143902

<151> 2004-05-13

<150> PCT/JP2005/008239

<151> 2005-04-28

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<170> PatentIn version 3.1

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gag ccc aag aag tac gca gtg acc gac gac tac cag ttg tcc aag cag	144
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Arg Thr Gly Gln Lys Cys Ala Leu Lys Leu Leu Tyr Asp Ser Pro Lys
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 Pro Thr Glu Arg Leu Thr Ile Thr Gln Phe Met Asn His Pro Trp Ile  
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Pro 65	Pro	Ala	Ala	Pro	Ser 70	Phe	Arg	Gln	Val	Ser 75	Cys	Leu	Lys	Glu	Leu 80
Val	Ala	Arg	Val	Leu 85	Gln	Arg	Leu	Cys	Glu 90	Arg	Gly	Ala	Lys	Asn 95	Val
Leu	Ala	Phe	Gly 100	Phe	Ala	Leu	Leu	Asp 105	Gly	Ala	Arg	Gly	Gly 110	Pro	Pro
Glu	Ala	Phe 115	Thr	Thr	Ser	Val	Arg 120	Ser	Tyr	Leu	Pro	Asn 125	Thr	Val	Thr
Asp 130	Ala	Leu	Arg	Gly	Ser	Gly 135	Ala	Trp	Gly	Leu	Leu 140	Leu	Arg	Arg	Val
Gly 145	Asp	Asp	Val	Leu	Val 150	His	Leu	Leu	Ala	Arg 155	Cys	Ala	Leu	Phe	Val 160
Leu	Val	Ala	Pro	Ser 165	Cys	Ala	Tyr	Gln	Val 170	Cys	Gly	Pro	Pro	Leu	Tyr 175
Gln	Leu	Gly	Ala 180	Ala	Thr	Gln	Ala	Arg 185	Pro	Pro	Pro	His	Ala 190	Ser	Gly
Pro	Arg	Arg 195	Arg	Leu	Gly	Cys	Glu 200	Arg	Ala	Trp	Asn	His 205	Ser	Val	Arg
Glu 210	Ala	Gly	Val	Pro	Leu	Gly 215	Leu	Pro	Ala	Pro	Gly 220	Ala	Arg	Arg	Arg
Gly 225	Gly	Ser	Ala	Ser	Arg 230	Ser	Leu	Pro	Leu	Pro 235	Lys	Arg	Pro	Arg	Arg 240
Gly	Ala	Ala	Pro	Glu 245	Pro	Glu	Arg	Thr	Pro 250	Val	Gly	Gln	Gly	Ser 255	Trp
Ala	His	Pro	Gly 260	Arg	Thr	Arg	Gly 265	Pro	Ser	Asp	Arg	Gly	Phe	Cys 270	Val
Val	Ser 275	Pro	Ala	Arg	Pro	Ala	Glu 280	Glu	Ala	Thr	Ser	Leu	Glu	Gly	Ala
Leu 290	Ser	Gly	Thr	Arg	His	Ser 295	His	Pro	Ser	Val	Gly 300	Arg	Gln	His	His

Ala Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr Pro  
 305 310 315 320

Cys Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser Gly  
 325 330 335

Asp Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg Pro  
 340 345 350

Ser Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly Ser  
 355 360 365

Arg Pro Trp Met Pro Gly Thr Pro Arg Arg Leu Pro Arg Leu Pro Gln  
 370 375 380

Arg Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn His  
 385 390 395 400

Ala Gln Cys Pro Tyr Gly Val Leu Leu Lys Thr His Cys Pro Leu Arg  
 405 410 415

Ala Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro Gln  
 420 425 430

Gly Ser Val Ala Ala Pro Glu Glu Glu Asp Thr Asp Pro Arg Arg Leu  
 435 440 445

Val Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly Phe  
 450 455 460

Val Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly Ser  
 465 470 475 480

Arg His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile Ser  
 485 490 495

Leu Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys Met  
 500 505 510

Ser Val Arg Asp Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly Cys  
 515 520 525

Val Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys Phe  
 530 535 540

Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser Phe  
 545 550 555 560

Phe	Tyr	Val	Thr	Glu	Thr	Thr	Phe	Gln	Lys	Asn	Arg	Leu	Phe	Phe	Tyr			
				565					570					575				
Arg	Lys	Ser	Val	Trp	Ser	Lys	Leu	Gln	Ser	Ile	Gly	Ile	Arg	Gln	His			
			580					585					590					
Leu	Lys	Arg	Val	Gln	Leu	Arg	Glu	Leu	Ser	Glu	Ala	Glu	Val	Arg	Gln			
		595					600					605						
His	Arg	Glu	Ala	Arg	Pro	Ala	Leu	Leu	Thr	Ser	Arg	Leu	Arg	Phe	Ile			
	610					615					620							
Pro	Lys	Pro	Asp	Gly	Leu	Arg	Pro	Ile	Val	Asn	Met	Asp	Tyr	Val	Val			
625					630					635					640			
Gly	Ala	Arg	Thr	Phe	Arg	Arg	Glu	Lys	Arg	Ala	Glu	Arg	Leu	Thr	Ser			
				645					650					655				
Arg	Val	Lys	Ala	Leu	Phe	Ser	Val	Leu	Asn	Tyr	Glu	Arg	Ala	Arg	Arg			
			660					665					670					
Pro	Gly	Leu	Leu	Gly	Ala	Ser	Val	Leu	Gly	Leu	Asp	Asp	Ile	His	Arg			
		675					680					685						
Ala	Trp	Arg	Thr	Phe	Val	Leu	Arg	Val	Arg	Ala	Gln	Asp	Pro	Pro	Pro			
	690					695					700							
Glu	Leu	Tyr	Phe	Val	Lys	Val	Asp	Val	Thr	Gly	Ala	Tyr	Asp	Thr	Ile			
705					710					715					720			
Pro	Gln	Asp	Arg	Leu	Thr	Glu	Val	Ile	Ala	Ser	Ile	Ile	Lys	Pro	Gln			
				725					730					735				
Asn	Thr	Tyr	Cys	Val	Arg	Arg	Tyr	Ala	Val	Val	Gln	Lys	Ala	Ala	His			
			740					745					750					
Gly	His	Val	Arg	Lys	Ala	Phe	Lys	Ser	His	Val	Ser	Thr	Leu	Thr	Asp			
		755					760					765						
Leu	Gln	Pro	Tyr	Met	Arg	Gln	Phe	Val	Ala	His	Leu	Gln	Glu	Thr	Ser			
	770					775					780							
Pro	Leu	Arg	Asp	Ala	Val	Val	Ile	Glu	Gln	Ser	Ser	Ser	Leu	Asn	Glu			
785					790					795					800			
Ala	Ser	Ser	Gly	Leu	Phe	Asp	Val	Phe	Leu	Arg	Phe	Met	Cys	His	His			
				805					810					815				

Ala Val Arg Ile Arg Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile Pro  
 820 825 830

Gln Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly Asp  
 835 840 845

Met Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu Leu  
 850 855 860

Arg Leu Val Asp Asp Phe Leu Leu Val Thr Pro His Leu Thr His Ala  
 865 870 875 880

Lys Thr Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys  
 885 890 895

Val Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp Glu  
 900 905 910

Ala Leu Gly Gly Thr Ala Phe Val Gln Met Pro Ala His Gly Leu Phe  
 915 920 925

Pro Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu Val Gln Ser  
 930 935 940

Asp Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr Phe  
 945 950 955 960

Asn Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe Gly  
 965 970 975

Val Leu Arg Leu Lys Cys His Ser Leu Phe Leu Asp Leu Gln Val Asn  
 980 985 990

Ser Leu Gln Thr Val Cys Thr Asn Ile Tyr Lys Ile Leu Leu Leu Gln  
 995 1000 1005

Ala Tyr Arg Phe His Ala Cys Val Leu Gln Leu Pro Phe His Gln  
 1010 1015 1020

Gln Val Trp Lys Asn Pro Thr Phe Phe Leu Arg Val Ile Ser Asp  
 1025 1030 1035

Thr Ala Ser Leu Cys Tyr Ser Ile Leu Lys Ala Lys Asn Ala Gly  
 1040 1045 1050

Met Ser Leu Gly Ala Lys Gly Ala Ala Gly Pro Leu Pro Ser Glu

1055		1060		1065
Ala Val Gln Trp Leu Cys His Gln Ala Phe Leu Leu Lys Leu Thr				
1070		1075		1080
Arg His Arg Val Thr Tyr Val Pro Leu Leu Gly Ser Leu Arg Thr				
1085		1090		1095
Ala Gln Thr Gln Leu Ser Arg Lys Leu Pro Gly Thr Thr Leu Thr				
1100		1105		1110
Ala Leu Glu Ala Ala Ala Asn Pro Ala Leu Pro Ser Asp Phe Lys				
1115		1120		1125
Thr Ile Leu Asp				
1130				

<210> 5  
 <211> 1149  
 <212> DNA  
 <213> Artificial

<220>  
 <223> A polynucleotide encoding an inactive variant of MAPKAPK3 (SEQ ID NO:2) which amino acid residues at positions 201 and 313 are both replaced to alanine from threonine

<400> 5  
 atggatggtg aaacagcaga ggagcagggg ggccctgtgc ccccgccagt tgcacccggc 60  
 ggacccggct tgggcggtgc tccggggggg cggcgggagc ccaagaagta cgcagtgacc 120  
 gacgactacc agttgtccaa gcaggtgctg ggcctgggtg tgaacggcaa agtgctggag 180  
 tgcttccatc ggcgcactgg acagaagtgt gccctgaagc tcctgtatga cagccccaag 240  
 gcccggcagg aggtagacca tcaactggcag gcttctggcg gccccatat tgtctgcatc 300  
 ctggatgtgt atgagaacat gcaccatggc aagcgctgtc tcctcatcat catggaatgc 360  
 atggaaggtg gtgagttggt cagcaggatt caggagcgtg gcgaccaggc tttcactgag 420  
 agagaagctg cagagataat gcgggatatt ggcaactgcca tccagtttct gcacagccat 480  
 aacattgccc accgagatgt caagcctgaa aacctactct acacatctaa ggagaaagac 540  
 gcagtgctta agctcaccga ttttggtttt gctaaggaga ccacccaaaa tgccctgcag 600  
 gccccctgct atactcccta ttatgtggcc cctgaggtcc tgggtccaga gaagtatgac 660  
 aagtcattgt acatgtggtc cctgggtgtc atcatgtaca tcctcctttg tggcttccca 720  
 cccttctact ccaacacggg ccaggccatc tccccgggga tgaagaggag gattcgctg 780  
 ggccagtacg gcttcccaaa tcctgagtgg tcagaagtct ctgaggatgc caagcagctg 840  
 atccgcctcc tggtgaagac agacccaca gagaggctga ccatcactca gttcatgaac 900

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caccctgga tcaaccaatc gatggtagt ccacaggccc cactccacac ggcccgagtg      960
ctgcaggagg acaaagacca ctgggacgaa gtcaaggagg agatgaccag tgccttggcc      1020
actatgcggg tagactacga ccaggtgaag atcaaggacc tgaagacctc taacaaccgg      1080
ctcctcaaca agaggagaaa aaagcaggca ggcagctcct ctgcctcaca gggctgcaac      1140
aaccagtag                                     1149

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<210> 6
<211> 382
<212> PRT
<213> Artificial

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<220>
<223> An inactive variant of MAPKAPK3 (SEQ ID NO:2) which amino acid re
      sidues at positions 201 and 313 are both replaced to alanine from
      threonine

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<400> 6

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Met Asp Gly Glu Thr Ala Glu Glu Gln Gly Gly Pro Val Pro Pro Pro
1          5          10          15

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Val Ala Pro Gly Gly Pro Gly Leu Gly Gly Ala Pro Gly Gly Arg Arg
          20          25          30

```

```

Glu Pro Lys Lys Tyr Ala Val Thr Asp Asp Tyr Gln Leu Ser Lys Gln
          35          40          45

```

```

Val Leu Gly Leu Gly Val Asn Gly Lys Val Leu Glu Cys Phe His Arg
          50          55          60

```

```

Arg Thr Gly Gln Lys Cys Ala Leu Lys Leu Leu Tyr Asp Ser Pro Lys
          65          70          75          80

```

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Ala Arg Gln Glu Val Asp His His Trp Gln Ala Ser Gly Gly Pro His
          85          90          95

```

```

Ile Val Cys Ile Leu Asp Val Tyr Glu Asn Met His His Gly Lys Arg
          100          105          110

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```

Cys Leu Leu Ile Ile Met Glu Cys Met Glu Gly Gly Glu Leu Phe Ser
          115          120          125

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Arg Ile Gln Glu Arg Gly Asp Gln Ala Phe Thr Glu Arg Glu Ala Ala
          130          135          140

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Glu Ile Met Arg Asp Ile Gly Thr Ala Ile Gln Phe Leu His Ser His
          145          150          155          160

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Asn Ile Ala His Arg Asp Val Lys Pro Glu Asn Leu Leu Tyr Thr Ser  
165 170 175

Lys Glu Lys Asp Ala Val Leu Lys Leu Thr Asp Phe Gly Phe Ala Lys  
180 185 190

Glu Thr Thr Gln Asn Ala Leu Gln Ala Pro Cys Tyr Thr Pro Tyr Tyr  
195 200 205

Val Ala Pro Glu Val Leu Gly Pro Glu Lys Tyr Asp Lys Ser Cys Asp  
210 215 220

Met Trp Ser Leu Gly Val Ile Met Tyr Ile Leu Leu Cys Gly Phe Pro  
225 230 235 240

Pro Phe Tyr Ser Asn Thr Gly Gln Ala Ile Ser Pro Gly Met Lys Arg  
245 250 255

Arg Ile Arg Leu Gly Gln Tyr Gly Phe Pro Asn Pro Glu Trp Ser Glu  
260 265 270

Val Ser Glu Asp Ala Lys Gln Leu Ile Arg Leu Leu Leu Lys Thr Asp  
275 280 285

Pro Thr Glu Arg Leu Thr Ile Thr Gln Phe Met Asn His Pro Trp Ile  
290 295 300

Asn Gln Ser Met Val Val Pro Gln Ala Pro Leu His Thr Ala Arg Val  
305 310 315 320

Leu Gln Glu Asp Lys Asp His Trp Asp Glu Val Lys Glu Glu Met Thr  
325 330 335

Ser Ala Leu Ala Thr Met Arg Val Asp Tyr Asp Gln Val Lys Ile Lys  
340 345 350

Asp Leu Lys Thr Ser Asn Asn Arg Leu Leu Asn Lys Arg Arg Lys Lys  
355 360 365

Gln Ala Gly Ser Ser Ser Ala Ser Gln Gly Cys Asn Asn Gln  
370 375 380

<210> 7  
<211> 1149  
<212> DNA  
<213> Artificial

<220>

<223> A polynucleotide encoding an active variant of MAPKAPK3 (SEQ ID NO:2) which amino acid residues at positions 201 and 313 are both replaced to glutamic acid from threonine

<400> 7  
atggatggtg aaacagcaga ggagcagggg ggccctgtgc ccccgccagt tgcacccggc 60  
ggacccggct tgggcggtgc tccggggggg cggcgggagc ccaagaagta cgcagtgacc 120  
gacgactacc agttgtccaa gcaggtgctg ggccctgggtg tgaacggcaa agtgctggag 180  
tgcttccatc ggcgcaactgg acagaagtgt gccctgaagc tcctgtatga cagccccaag 240  
gcccggcagg aggtagacca tcactggcag gcttctggcg gcccctatat tgtctgcatc 300  
ctggatgtgt atgagaacat gcaccatggc aagcgctgtc tcctcatcat catggaatgc 360  
atggaaggtg gtgagttggt cagcaggatt caggagcgtg gcgaccaggc tttcactgag 420  
agagaagctg cagagataat gcgggatatt ggcaactgcca tccagtttct gcacagccat 480  
aacattgccc accgagatgt caagcctgaa aacctactct acacatctaa ggagaaagac 540  
gcagtgctta agctcaccga ttttggtctt gctaaggaga ccacccaaaa tgccctgcag 600  
gagccctgct atactcccta ttatgtggcc cctgagggtc tgggtccaga gaagtatgac 660  
aagtcattgt acatgtgggt cctgggtgtc atcatgtaca tcctcctttg tggcttccca 720  
cccttctact ccaacacggg ccaggccatc tccccgggga tgaagaggag gattcgcttg 780  
ggccagtacg gcttcccca tcttgagtgg tcagaagtct ctgaggatgc caagcagctg 840  
atccgcctcc tggtgaagac agacccaca gagaggctga ccatcactca gttcatgaac 900  
caccctgga tcaaccaatc gatggtagtg ccacaggagc cactccacac ggcccagatg 960  
ctgcaggagg acaaagacca ctgggacgaa gtcaaggagg agatgaccag tgccttggtc 1020  
actatgcggg tagactacga ccagggtgaag atcaaggacc tgaagacctc taacaaccgg 1080  
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aaccagtag 1149

<210> 8  
<211> 382  
<212> PRT  
<213> Artificial

<220>  
<223> An active variant of MAPKAPK3 (SEQ ID NO:2) which amino acid residues at positions 201 and 313 are both replaced to glutamic acid from threonine

<400> 8  
Met Asp Gly Glu Thr Ala Glu Glu Gln Gly Gly Pro Val Pro Pro Pro  
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Val Ala Pro Gly Gly Pro Gly Leu Gly Gly Ala Pro Gly Gly Arg Arg

20					25					30					
Glu	Pro	Lys	Lys	Tyr	Ala	Val	Thr	Asp	Asp	Tyr	Gln	Leu	Ser	Lys	Gln
		35					40					45			
Val	Leu	Gly	Leu	Gly	Val	Asn	Gly	Lys	Val	Leu	Glu	Cys	Phe	His	Arg
	50					55					60				
Arg	Thr	Gly	Gln	Lys	Cys	Ala	Leu	Lys	Leu	Leu	Tyr	Asp	Ser	Pro	Lys
65					70					75					80
Ala	Arg	Gln	Glu	Val	Asp	His	His	Trp	Gln	Ala	Ser	Gly	Gly	Pro	His
				85					90					95	
Ile	Val	Cys	Ile	Leu	Asp	Val	Tyr	Glu	Asn	Met	His	His	Gly	Lys	Arg
			100					105					110		
Cys	Leu	Leu	Ile	Ile	Met	Glu	Cys	Met	Glu	Gly	Gly	Glu	Leu	Phe	Ser
		115					120					125			
Arg	Ile	Gln	Glu	Arg	Gly	Asp	Gln	Ala	Phe	Thr	Glu	Arg	Glu	Ala	Ala
	130					135					140				
Glu	Ile	Met	Arg	Asp	Ile	Gly	Thr	Ala	Ile	Gln	Phe	Leu	His	Ser	His
145						150					155				160
Asn	Ile	Ala	His	Arg	Asp	Val	Lys	Pro	Glu	Asn	Leu	Leu	Tyr	Thr	Ser
				165					170					175	
Lys	Glu	Lys	Asp	Ala	Val	Leu	Lys	Leu	Thr	Asp	Phe	Gly	Phe	Ala	Lys
			180					185					190		
Glu	Thr	Thr	Gln	Asn	Ala	Leu	Gln	Glu	Pro	Cys	Tyr	Thr	Pro	Tyr	Tyr
		195					200					205			
Val	Ala	Pro	Glu	Val	Leu	Gly	Pro	Glu	Lys	Tyr	Asp	Lys	Ser	Cys	Asp
	210					215					220				
Met	Trp	Ser	Leu	Gly	Val	Ile	Met	Tyr	Ile	Leu	Leu	Cys	Gly	Phe	Pro
225					230					235					240
Pro	Phe	Tyr	Ser	Asn	Thr	Gly	Gln	Ala	Ile	Ser	Pro	Gly	Met	Lys	Arg
				245					250					255	
Arg	Ile	Arg	Leu	Gly	Gln	Tyr	Gly	Phe	Pro	Asn	Pro	Glu	Trp	Ser	Glu
			260					265					270		

Val Ser Glu Asp Ala Lys Gln Leu Ile Arg Leu Leu Leu Lys Thr Asp  
275 280 285

Pro Thr Glu Arg Leu Thr Ile Thr Gln Phe Met Asn His Pro Trp Ile  
290 295 300

Asn Gln Ser Met Val Val Pro Gln Glu Pro Leu His Thr Ala Arg Val  
305 310 315 320

Leu Gln Glu Asp Lys Asp His Trp Asp Glu Val Lys Glu Glu Met Thr  
325 330 335

Ser Ala Leu Ala Thr Met Arg Val Asp Tyr Asp Gln Val Lys Ile Lys  
340 345 350

Asp Leu Lys Thr Ser Asn Asn Arg Leu Leu Asn Lys Arg Arg Lys Lys  
355 360 365

Gln Ala Gly Ser Ser Ser Ala Ser Gln Gly Cys Asn Asn Gln  
370 375 380

<210> 9  
<211> 6  
<212> PRT  
<213> Artificial

<220>  
<223> Partial sequence of TERT (SEQ ID NO:4) , which is highly homologous to that of MAPKAPK3 (SEQ ID NO:2)

<400> 9

Pro Pro Pro Ala Ala Pro  
1 5

<210> 10  
<211> 6  
<212> PRT  
<213> Artificial

<220>  
<223> Partial sequence of MAPKAPK3 (SEQ ID NO:2) , which is highly homologous to that of TERT (SEQ ID NO:4)

<400> 10

Pro Pro Pro Val Ala Pro  
1 5

<210> 11  
<211> 6  
<212> PRT  
<213> Artificial

<220>  
<223> Partial sequence of TERT (SEQ ID NO:4) , which is highly homologous to that of MAPKAPK3 (SEQ ID NO:2)

<400> 11

Ala Pro Gly Ala Arg Arg  
1 5

<210> 12  
<211> 6  
<212> PRT  
<213> Artificial

<220>  
<223> Partial sequence of MAPKAPK3 (SEQ ID NO:2) , which is highly homologous to that of TERT (SEQ ID NO:4)

<400> 12

Ala Pro Gly Gly Arg Arg  
1 5

<210> 13  
<211> 5  
<212> PRT  
<213> Artificial

<220>  
<223> Partial sequence identical in the sequences of TERT (SEQ ID NO:4) and MAPKAPK3 (SEQ ID NO:2)

<400> 13

Ala Arg Val Leu Gln  
1 5